Fluid resuscitation in trauma: What you need to know

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ABSTRACT: There have been numerous changes in resuscitation strategies for severely injured patients over the last several decades. Certain strategies, such as aggressive crystalloid resuscitation, have largely been abandoned because of the high incidence of complications and worsening of trauma-induced coagulopathy. Significant emphasis has been placed on restoring a normal coagulation profile with plasma or whole blood transfusion. In addition, the importance of the lethal consequences of trauma-induced coagulopathy, such as hyperfibrinolysis, has been easily recognized by the use of viscoelastic testing, and its treatment with tranexamic acid has been extensively studied. Furthermore, the critical role of early intravenous calcium administration, even before blood transfusion administration, has been emphasized. Other adjuncts, such as fibrinogen supplementation with fibrinogen concentrate or cryoprecipitate and prothrombin complex concentrate, are being studied and incorporated in some of the institutional massive transfusion protocols. Finally, balanced blood component transfusion (1:1:1 or 1:1:2) and whole blood have become commonplace in trauma centers in North America. This review provides a description of recent developments in resuscitation and a discussion of recent innovations and areas for future investigation. (*J Trauma Acute Care Surg.* 2025;98: 20–29. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Blood; massive transfusion; resuscitation; trauma-induced coagulopathy; hemorrhage.

The resuscitation of trauma patients has evolved significantly in recent years. Certain dogmatic practices were found to be deleterious and largely abandoned, while new frontiers are being explored as the complexities of trauma-induced coagulopathy are being discerned. This review aims to provide an overview of the contemporary literature regarding fluid resuscitation in trauma and introduce future directions and potential investigations.

LIMITING CRYSTALLOIDS

Hemorrhagic shock results in cellular insults leading to deficits in tissue and end-organ perfusion, which can, at least in part, be mitigated by the administration of intravenous fluids as cardiac output is augmented. Crystalloid solutions have been used for decades as the main resuscitation fluid for traumatic shock.[1,2] Previous editions of the Advanced Trauma Life Support course encouraged the administration of 2 L of crystalloid in hemodynamically unstable trauma patients when starting the resuscitation process. It was also common practice to replace each milliliter of blood lost with 3 mL of crystalloid.[3]

Currently, there is growing evidence about the deleterious effects of aggressive crystalloid resuscitation, which may result in uncontrolled hemorrhage due to increased arterial and venous pressure, decreased intestinal perfusion, intra-abdominal hypertension, and abdominal compartment syndrome, culminating with multiple organ failure.[4] Aggressive crystalloid resuscitation is also associated with coagulopathy due to depletion of clotting factors and acidosis, resulting in higher mortality rates.[5–8]

Crystalloid solutions can reduce a patient's core temperature and may further exacerbate hypothermia. An infusion of 2 L of room-temperature crystalloid decreases the body temperature in normothermic adults, while blood transfused at the same temperature has minimal effects.[9] Lactated Ringer's and normal saline are relatively acidotic solutions with a pH of 6.5 and 5.5, respectively, and can worsen acidosis.[10] Another deleterious effect of crystalloids is severe electrolyte derangements as a result of the electrolyte composite in these solutions, along with the activation of the renin-angiotensin-aldosterone system coupled with the additional release of antidiuretic hormone after injury.[11]

While overresuscitation is associated with poor outcomes, the question is whether less aggressive strategies result in improved outcomes. Schmidt et al.[12] subjected male rats to uncontrolled hemorrhage and randomized them to different treatment arms: no fluid resuscitation, permissive hypotension, and normotensive resuscitation with lactated Ringer's. Animals undergoing normotensive resuscitation experienced higher intra-abdominal blood loss. Cardiac output and end-organ perfusion to the brain, kidneys, liver, gastrointestinal system, and heart were comparable in the permissive hypotension and normotensive resuscitation groups.

Schreiber et al.[13] randomized 192 hypotensive trauma patients to either controlled resuscitation (250-mL bolus intravenous in the field to maintain a systolic blood pressure [SBP] of 70 mm Hg) or standard resuscitation (intravenous fluids to maintain an SBP of 100 mm Hg). Mortality at 24 hours and in-hospital mortality were similar. More patients in the controlled resuscitation group developed renal injury but without statistical

Submitted: July 8, 2024, Revised: July 9, 2024, Accepted: July 9, 2024, Published online: August 30, 2024.

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DOI: 10.1097/TA.0000000000004456

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significance. The study demonstrated that controlled resuscitation was achievable and safe.[13]

Animal models of hemorrhagic shock have demonstrated that hypertonic solutions can decrease inflammation by attenuating leukocyte sequestration and neutrophil activity compared with isotonic or slightly hypotonic crystalloids.[14,15] In addition, the smaller volume required to achieve end-organ perfusion may also have contributed to the lower incidence of multiple organ failure and mortality observed in animal studies.[16,17] Enthusiasm for hypertonic saline was tempered by a multicenter randomized trial wherein 853 hypotensive trauma patients were given either 250 mL bolus of 7.5% saline, 7.5% saline, 6% dextran 70, or 0.9% normal saline as the initial resuscitation fluid in the prehospital setting.[18] While there were no differences in 28-day survival between the treatment arms, mortality was higher in the subset of patients who received either 7.5% saline, or 7.5% saline and 6% dextran 70 without additional blood transfusions. The findings resulted in the study being terminated early. The authors postulated that the higher mortality occurred in the subset of patients who received hypertonic fluids either due to exacerbation of hemorrhage or due to delayed recognition of shock followed by transfusions.

The most recent Advanced Trauma Life Support version emphasizes the early administration of blood products with a smaller volume of crystalloids or without any crystalloids given.[19]

BLOOD PRODUCT COMPONENTS

Blood products allow for improved oxygen delivery, which mitigates issues related to tissue ischemia and systemic lactic acidosis. Transfusion of blood components with packed red blood cells (PRBCs), plasma, and platelets was described in the 1970s and quickly adopted in clinical practice in the following decades.[20,21] Transfusing patients with blood components in a certain ratio to "reconstitute" whole blood may help achieve hemostasis, whereas transfusing PRBCs alone cannot.[22]

The concept of damage-control resuscitation, initially described by Holcomb et al.[23] in 2007, aims to mitigate the development of acidosis and coagulopathy by the early administration of blood products and rapid hemorrhage control.[24,25] In their report, the authors emphasized targeting an SBP of 90 mm Hg to prevent rebleeding and supplementing PRBC transfusions with plasma in a 1:1 or 1:2 ratio.[23]

The Prospective, Observational, Multicenter, Major Trauma Transfusion Study (PROMMTT) provided insights about the timing of component transfusions using minute-to-minute data from 10 Level I trauma centers.[26] The authors found that earlier administration of higher plasma (adjusted hazard ratio, 0.31 [95% confidence interval, 0.16–0.58]) and platelets (adjusted hazard ratio, 0.55 [95% confidence interval, 0.31–0.98]) ratios to PRBCs were associated with decreased mortality among those receiving at least 3 U of any blood product during the first 24 hours from admission. Interestingly, the timing of additional component transfusions after 24 hours was not associated with altered mortality rates.

Subsequently, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial aimed to compare the effectiveness of transfusing patients with plasma, platelets, and red blood cells according to two resuscitation strategies: 1:1:1 and 1:1:2.[27] Transfusions ceased when either hemostasis was achieved, the patient expired, or care was deemed futile. While mortality at 24 hours and 30 days was comparable in both arms of the study, deaths due to exsanguination were lower in the 1:1:1 arm (9.2% vs. 14.6%, $p = 0.03$). In addition, those patients were more likely to achieve hemostasis (86% vs. 78%, $p < 0.01$). The 1:1:1 strategy did not result in more complications and was deemed safe.

The PROPPR trial emphasized the importance of balanced resuscitation with component therapy. Presumably, the relatively higher transfusions of plasma and platelets in the 1:1:1 cohort resulted in the differences observed in the rates of deaths, specifically due to exsanguination and time to hemostasis. While a 1:1 transfusion ratio of plasma to PRBCs is often used, ratios that use relatively higher amounts of PRBCs, such as 1:2 or 1:3, have been associated with comparable mortality rates.[28]

MASSIVE TRANSFUSION PROTOCOLS

Although it has been established that balanced transfusions with appropriate ratios are imperative, consistently executing these practices is difficult. The implementation of massive transfusion protocols (MTPs) allows trauma surgeons to deliver blood products rapidly and effectively in a systematic fashion once massive hemorrhage has been identified and resources are available at a given institution. Deviations from MTPs occur often.[24,25] However, compliance with MTP is associated with better outcomes.[29]

The ability to predict which patients would benefit from the activation of the massive transfusion protocol is difficult. Different scoring systems have been described in the literature. The Assessment of Blood Consumption (ABC) score, first described in 2009, is a commonly used scoring system.[30] It consists of four variables: penetrating mechanism of injury, a positive focused assessment sonography for trauma (FAST), admission SBP of ≤90 mm Hg, and admission heart rate (HR) of ≥120 beats per minute (Table 1). A point is given for each qualifying criterion, for a maximum of 4 points. A score of 2 or greater is associated with higher rates of massive transfusion. A multicenter study validated these findings across three institutions, with the sensitivity ranging from 75% to 90% and the specificity ranging from 67% to 88%.[31] Expanded use of the ABC score has been described in the prehospital setting as well.[32]

Another scoring system used is the Revised Assessment of Bleeding and Transfusion (RABT) score. Instead of using admission SBP and HR as separate variables, the RABT score

TABLE 1. Comparison of Scoring Criteria

	ABC Score	RABT Score
Admission HR >120 mm Hg	✔	
Admission SBP <90 mm Hg	✔	
Penetrating mechanism	✔	✔
Positive FAST	✔	✔
Presence of a pelvic fracture		✔
SI >0.9		✔

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combines these elements into a shock index (SI), calculated by dividing the HR by the SBP.[33] A SI greater than 0.9 predicts the need for massive transfusion.[34] Additional criteria include a penetrating mechanism of injury, a positive FAST, and the presence of a pelvic fracture. Like the ABC score, a point is assigned for each criterion, with a score of 2 or more corresponding to an increased need for MTP. Compared with the ABC score, RABT has a reported higher sensitivity (RABT, 78% vs. ABC, 69%) and specificity (RABT, 91% vs. ABC, 82%).[35]

With the advent of artificial intelligence and machine learning, there may be additional opportunities to better identify patients who would benefit from MTP activation. Strickland et al.[36] described a series of models that include the patient's age, mechanism of injury, admission vital signs, admission Glasgow Coma Scale, FAST results, and pelvic x-ray findings. These models had higher sensitivity than the ABC and RABT scoring systems but similar specificity.

While there has been extensive literature about when to initiate MTP, there is little written about when to cease it. This becomes an important area of investigation considering that MTP utilization is resource intensive, and blood is generally of limited supply. While achieving hemostasis is one end point, futility is another. Attempts to define futility have been unsuccessful, as many patients will survive despite high transfusion requirements.[37]

CALCIUM SUPPLEMENTATION

Large-volume resuscitation of blood components allows for the repletion of coagulation factors required for hemostasis; however, it may result in hypocalcemia, which has physiologic implications. Citrate anticoagulant is present in stored blood, which binds to ionized calcium, decreasing serum calcium levels among patients receiving large blood transfusions. Byerly et al.[38] identified higher PRBCs and plasma transfusions as independent predictors of severe hypocalcemia. The incidence of hypocalcemia in MTP has been reported to be as high as 85% to 97%.[30] In addition, elevated levels of lactate from tissue injury and reperfusion can bind and chelate calcium, further contributing to hypocalcemia.[39]

Calcium is critical in maintaining neuromuscular and cardiovascular membrane stability and, thus, is necessary in facilitating electrical conduction and myocardial activity.[40] Disturbances may manifest as arrhythmias and heart failure. Calcium has also been implicated in pathways that involve platelet function and hemostasis. Low calcium levels have been associated with higher morbidity and mortality rates.[41] The Joint Trauma System guideline on damage-control resuscitation recommends early calcium administration with either calcium gluconate or calcium chloride, with additional doses given after every 4 U of blood transfused.[42]

The Clinical Assessment of Low Calcium in Trauma (CALCIUM) is a multicenter, prospective, observational study that will help elucidate the true incidence of hypocalcemia and its relationship with transfusions and related outcomes.[43]

VISCOELASTIC ASSAYS

Thrombomelastography (TEG) and rotational thromboelastometry (ROTEM) are commonly used to assess coagulation function. These assays determine the components required to create and sustain a clot by quantifying the time taken to initiate clot formation, clot kinetics, clot strength, and clot lysis. While the mechanics of how these assays are performed differ, the principles are similar.

Since the first description of TEG in 1940, TEG and ROTEM have been integrated into the assessment of severely injured patients and used liberally in trauma centers to assist in the diagnosis and management of trauma-induced coagulopathy.[44] Findings from these assays often offer additional insights into a patient's coagulation function but correlate poorly with conventional laboratory tests, such as the international normalized ratio (INR) and partial thromboplastin time.

The concept of trauma-induced coagulopathy refers to the altered coagulation response after trauma. Moore et al.[45] described a spectrum of phenotypes ranging from hypercoagulable to hypocoagulable. Hypercoagulable phenotypes can be observed relatively early after injury, even in the setting of hemorrhage. This variation in phenotypes is observed because of platelet dysfunction, fibrinogen depletion, increased or decreased thrombin generation, and alternations in fibrinolysis.

Coleman et al.[46] used a wide array of TEG-based assays to characterize differences between male and premenopausal female subjects. Females were relatively more hypercoagulable, with quicker clot formation and propagation and increased clot strength. Fibrinolysis, however, was similar. These differences in coagulation may explain why severely injured female patients have lower mortality rates compared with their male counterparts.[47]

Whereas MTP has been a means to mitigate trauma-induced coagulopathy by empirically repleting clotting factors and providing platelets, resuscitation guided by TEG or ROTEM may potentially address specific coagulation deficits and variations in coagulation phenotypes observed after injury. This latter strategy is often called goal-directed resuscitation. Based on the identified deficiency, different agents may be used to correct coagulopathy, including coagulation factors replacement, fibrinogen, cryoprecipitate, desmopressin, antifibrinolytics (e.g., tranexamic acid [TXA]), or additional blood products.[48]

Tapia et al.[49] described their institutional experience using TEG to guide resuscitation at Ben Taub General Hospital. Before MTP was implemented, where blood products were transfused in an algorithmic fashion, TEGs were routinely obtained, and blood products were administered according to TEG data. The authors found that TEG-directed resuscitation was superior to MTP in patients presenting with penetrating trauma, while mortality was similar among patients with blunt trauma. Gonzalez et al.[50] performed a randomized controlled trial where severely injured patients were randomized to receive MTP directed by TEG or conventional coagulation assays, including the INR, partial thromboplastin time, platelet count, and fibrinogen concentration. Although both cohorts consumed a similar number of PRBCs, those who received TEG-guided resuscitation required fewer units of plasma and fewer platelets. Mortality in the TEG group was also substantially lower.

While viscoelastic testing may better characterize coagulopathy, it does not assess interactions with the endothelial environment, which has implications for trauma-induced coagulopathy. In addition, platelet inhibition and dysfunction cannot be analyzed well in standard TEGs and require platelet mapping technology.[47]

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WHOLE BLOOD

The United States Army used whole blood during World War I, World War II, and the Korean War. However, it was less often used with the advent of blood component separation. Whole blood has again gained popularity in recent years and is the subject of several ongoing investigations.

Whole blood is available in two formulations: warm fresh whole blood or low-titer type O whole blood (LTOWB). As opposed to warm fresh whole blood, LTOWB is a Food and Drug Administration–approved product. Compared with component therapy, LTOWB offers better oxygen-carrying capacity with lower volumes and is associated with better coagulation.[25] In addition, to better mitigate the pathophysiologic issues resulting from hemorrhagic shock, LTOWB has logistical advantages that make it an attractive option in certain settings. While blood components may need to be frozen and thawed, LTOWB only requires refrigeration. However, the cold storage processing of LTOWB may degenerate its hemostatic properties.[51,52]

Low-titer type O whole blood has recently been introduced in the civilian setting with reasonable success. Through a prospective multicenter study involving 14 trauma centers in the United States, Hazelton et al.[53] demonstrated that trauma patients who received LTOWB as part of their initial resuscitation had a lower mortality rate and fewer bleeding complications compared with those who received exclusively blood component therapy. The rates of in-hospital complications, including acute kidney injury, deep vein thrombosis, pulmonary embolism, and pulmonary complications, were similar. Torres et al.[54] analyzed the Trauma Quality Improvement Program (TQIP) data and compared the outcomes of those who received MTP with blood component therapy or whole blood. Patients receiving whole blood had improved 24-hour and 30-day survival. With these promising results, some have implemented LTOWB in the prehospital setting. While experience is limited, it has been shown that the use of whole blood in the prehospital setting is associated with improvement in the SI and reduction in MTP utilization.[55]

Despite widespread enthusiasm, there are limitations to using whole blood. There is limited availability, with only a few units allocated to trauma centers periodically. Refrigerating and storing whole blood are associated with hemolysis, alterations in the coagulation profile, and platelet sequestration.[56–58] In addition, because of concerns about alloimmunization, there has been a reluctance to give females of childbearing age whole blood. However, this concern may be overstated as the rate of alloimmunization among Rhesus factor–negative women ranges from 3% to 19%, and among pregnant patients who become alloimmunized, there is a 4% risk of fetal demise.[59]

PREHOSPITAL PLASMA

With a greater focus on addressing hemorrhagic shock–associated coagulopathy, the use of prehospital plasma has been recently evaluated. Plasma has been shown to attenuate the inflammatory response typically seen as a result of hemorrhagic shock and lessen the severity of endothelial damage.[60,61]

The Control of Major Bleeding After Trauma (COMBAT) trial was a pragmatic randomized trial involving hypotensive trauma patients who received either plasma or normal saline during ground transport from the scene to the trauma center.[62] The authors could not show a mortality benefit in those who received plasma; however, plasma's noninferiority was demonstrated. The authors speculated that the benefit of prehospital blood product administration could be potentially appreciated in patients who require longer transport times.

The Prehospital Air Medical Plasma (PAMPer) trial provided additional insights into the efficacy of prehospital plasma administration.[63] This pragmatic, multicenter, cluster-randomized trial involved trauma patients at risk for hemorrhagic shock who underwent air medical transport to one of nine participating trauma centers. Patients who had at least one episode of hypotension were randomized to the treatment arm receiving 2 U of thawed plasma or to the standard of care arm. With 523 patients enrolled, the investigators noted a lower 30-day mortality rate in the plasma group (23.2% vs. 33.0%). Similar results were also appreciated in a subset of patients with traumatic brain injury. In addition, those who received prehospital plasma required a smaller volume of blood products during the first 24 hours after hospital admission. It should be noted that those who received plasma also received a smaller volume of crystalloids.

Although the results of the COMBAT and PAMPer trials appear to be conflicting, findings from post hoc analyses from both trials allow for reconciliation. Those who sustained blunt trauma were coagulopathic and required at least 20 minutes to be transported to the hospital from injury appear to benefit from prehospital plasma.[64]

The Resuscitation with Pre-Hospital Blood Products (RePHILL) trial, a multicenter study conducted in the United Kingdom, was recently published.[65] Hypotensive patients were randomized to receive 2 U of PRBCs, two packs of lyophilized plasma (a formulation of freeze-dried plasma), or 1 L of normal saline. The composite outcome, which included mortality and lactate clearance, was similar. Critics have argued that the composite outcome was not clinically relevant, given the inclusion of lactate, and that the trial was likely underpowered. The authors, however, showed that it was logistically possible to use lyophilized plasma.

Understanding which patients would benefit from prehospital plasma administration becomes imperative, as it requires significant resource allocation.

DRIED PLASMA

Dried plasma formulations have mostly been manufactured, used, and studied in Europe. Freeze-dried plasma, also known as dried plasma, is a feasible alternative to plasma. The dried formulation allows for a longer shelf life and remains stable in varying temperatures.[66] Dried plasma can be rehydrated with water and administered in the field without the need for specialized equipment. The method of drying plasma is also known as spray drying, which refers to using a pressurized gas chamber to create the product.[67] The feasibility of dried plasma was reinforced by a study performed by Mitra et al.[68] After transfusing red blood cells, patients received Lyoplas N-w, a brand of freeze-dried plasma, or standard care. With only 20 patients enrolled in the study, the authors were not able to draw any conclusions about clinical outcomes but were able to demonstrate feasibility, nonetheless.

The Prehospital Lyophilized Plasma Transfusion for Trauma-Induced Coagulopathy in Patients at Risk for Hemorrhagic

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Shock (PREHO-PLYO), a multicenter trial in France, aimed to characterize the impact of lyophilized plasma on trauma-induced coagulopathy.[69] Patients were randomized to receive up to 4 U of lyophilized plasma or a normal saline infusion in addition to several blood tests obtained at the time of hospital arrival. While the study showed no difference in the INR, its primary outcome showed that lyophilized plasma in the prehospital setting was safe and feasible.

LIQUID PLASMA

Fresh frozen plasma must be thawed before it can be used, and any thawed units that go unused within 5 days must be discarded. The waste of thawed plasma is a major issue in trauma centers worldwide. An alternative to thawed plasma is liquid plasma, which is not frozen and can be stored for several weeks. Smith et al. [70] reported that a unit of thawed plasma was wasted within 1.3 to 1.8 days, while a unit of liquid plasma was wasted every 36.5 days. The cost per unit was identical. [70]

Liquid plasma may improve hemostatic properties compared with thawed plasma. Matijevic et al.[71] compared several coagulation parameters between thawed plasma (obtained at day 0 and day 5 after thawing) and liquid plasma (obtained at days 0, 5, 10, 20, and 26). Liquid plasma was associated with greater thrombin and clot formation and retained more than 88% of clotting factor levels.

Another inherent property of liquid plasma that makes it attractive is its immediate availability and the fact it does not need to be thawed. A Level 1 trauma center reported their initial experience and noted that there was better MTP ratio compliance with liquid plasma administration.[72] The time to transfuse the first unit of plasma decreased by 49 minutes after liquid plasma was introduced in their trauma program. In addition, there was a lower incidence of acute kidney injury, and more patients recovered within 28 days from injury. The sample size was too small to draw substantial conclusions about the associations between acute kidney injury and recovery. However, the authors postulated that these differences may have occurred because of earlier plasma transfusion.

Fadeyi et al.[73] compared 178 patients who received liquid plasma with 270 patients who received thawed plasma and could not show a difference in the 24-hour mortality rate. Secondary outcomes of the study included in-hospital mortality and the need for intensive care unit admission, which were similar between groups. Another study using the TQIP database matched 107 patients who received liquid plasma to 214 patients who were transfused fresh frozen plasma.[74] Similar to other studies, the cohorts were similar concerning 24-hour (2.8% vs. 3.7%) and in-hospital (16.8% vs. 20.1%) mortality. It is possible that these studies were generally underpowered to detect a difference in mortality. While liquid plasma may be seen as a promising alternative to fresh frozen plasma, its impact on clinical outcomes has yet to be demonstrated.

TRANEXAMIC ACID

Tranexamic acid competitively inhibits the lysine receptor on plasminogen and prevents plasminogen's active form, plasmin, from degenerating clot.[75] Thus, TXA helps achieve hemostasis by preventing plasmin activation. A large body of literature in elective surgical cases shows that TXA is associated with lower transfusion requirements, which served as the premise of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial.[76] This international study involved 40 countries and enrolled patients who either had evidence of significant hemorrhage, as defined by an SBP of ≤90 mm Hg or HR of ≥110, or those at risk for significant hemorrhage. There was no stringent definition of what constituted significant hemorrhage, and this, instead, was at the provider's discretion. The treatment group received 1 g of TXA infused over 10 minutes, followed by 1 g infused over 8 hours, while the placebo group received normal saline. All-cause mortality was significantly lower in the TXA cohort (TXA, 14.5% vs. placebo, 16.0%). Mortality due to hemorrhage was also lower in the TXA group (TXA, 4.9% vs. placebo, 5.7%). The observed mortality benefit occurred in patients who received TXA within 3 hours of injury. The incidence of vascular thrombotic events, including myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis, was similar in both groups. While the findings of the CRASH-2 trial seemed to encourage TXA use, many criticized the seemingly arbitrary criteria for enrolling patients and inconsistent randomization. The study did not capture how severely injured the patients were, and given that only half of the study subjects received blood products, there is reason to suspect that many were not severely injured.

Subsequent studies have questioned the beneficial effects of TXA on outcomes, and some have implicated TXA in the formation of venous thromboembolism.[77,78]

Morrison et al.[79] investigated the relationship between TXA and mortality in the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study. Patients admitted to a hospital in Southern Afghanistan were included if they received at least 1 U of PRBCs within 24 hours of admission after combat-related injury. Earlier in the study period, patients received TXA at the discretion of a surgeon or anesthesiologist, while, later on, patients received TXA if there was evidence of hyperfibrinolysis. Those who received TXA had a lower unadjusted mortality (17.4% vs. 23.9%), which remained low after adjusting for injury severity (25.2% vs. 22.5%). The largest survival benefit was seen in the subset of patients who received massive transfusion, defined as receiving at least 10 U of PRBCs within 24 hours. The rates of deep vein thrombosis and pulmonary embolism were higher in the TXA cohort. Another study on US military casualties from 2011 to 2015 demonstrated that TXA administration was an independent risk factor for venous thromboembolism.[80]

The investigators of the Prehospital Tranexamic Acid for Severe Trauma (PATCH) trial aimed to elucidate the role of TXA in a mature prehospital trauma system.[81] Based in Australia, New Zealand, and Germany, patients scoring 3 or more points on the Coagulopathy of Severe Trauma score received either a 1-g bolus of TXA followed by an infusion of 1 g over 8 hours or a placebo. The study's primary outcome was survival with a favorable function outcome 6 months after injury, as defined by a Glasgow Outcome Scale Extended level of 5 (corresponding to "lower moderate disability") or more. Those who received TXA had similar functional outcomes compared with those in the placebo group (TXA, 53.7% vs. placebo, 53.5%). Mortality 6 months after injury, specifically due to bleeding, was similar (TXA, 5.6% vs. placebo, 8.3%). The rates

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of vascular occlusive events, including deep vein thrombosis, pulmonary embolism, myocardial infarction, and ischemic strokes, were comparable. The PATCH trial effectively questioned the role of TXA in improving outcomes.

The Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport (STAAMP) trial was a multicenter, double-blinded, randomized clinical trial.[77] Patients who had at least one episode of hypotension (SBP, <110 mm Hg) or an HR of ≥110 beats per minute received either a 1-g bolus of TXA over 10 minutes or a placebo. Upon arrival at the trauma center, patients received either no additional TXA (abbreviated dosing), 1 g of TXA infused over 8 hours (standard dosing), or an additional 1-g bolus followed by a 1-g infusion over 8 hours. With more than 900 patients enrolled, the investigators were unable to detect a difference in 30-day mortality when comparing all patients who received any formulation of TXA compared with placebo. Still, they did notice a lower mortality rate in the cohort that received a repeat bolus of 1-g TXA followed by a 1-g infusion (7.3% vs. 10.0%) and in those with an SBP of ≤70 mm Hg (18.5% vs. 35.5%).

The aforementioned studies, as summarized in Table 2, show that the benefit of TXA is unclear. Perhaps the differential response with TXA administration stems from the concept that there are different fibrinolytic phenotypes among trauma patients, which was not investigated in these studies. Moore et al.[82] described a spectrum of fibrinolysis among patients following injury, wherein some patients demonstrate hyperfibrinolysis, defined as lysis at 30 minutes ≥3%, while others exhibit fibrinolysis shutdown, defined as lysis at 30 minutes ≤0.8%. Exogenous supplementation of TXA in those with fibrinolysis shutdown can result in organ dysfunction and death.[83]

CRYOPRECIPITATE AND FIBRINOGEN CONCENTRATE

Fibrinogen is a precursor of fibrin and is necessary for establishing a fibrin clot. It is quickly depleted after hemorrhage because of consumption and fibrinolysis. Levels below 100 mg/dL are strongly associated with a higher risk of mortality.[84] Repletion of fibrinogen can be accomplished either through the administration of cryoprecipitate or fibrinogen concentrate.

The Fibrinogen Early In Severe Trauma studY (FEISTY) was an Australian, multicenter randomized controlled trial that sought to compare how quickly fibrinogen levels could be repleted with fibrinogen concentrate compared with pools of cryoprecipitate.[85] Patients received either product if the FIBTEM A5, a functional fibrinogen assay, suggested fibrinogen deficiency and further dosing was guided by the assay set by the trial protocol. The study's primary outcome was the time to commencement of fibrinogen replacement, which was quicker in the fibrinogen concentrate arm. Fibrinogen levels increased appropriately in both arms. The mortality rate was higher in the cohort that received fibrinogen concentrate. The FESITY trial established that fibrinogen supplementation with fibrinogen concentrate was feasible; however, it was not powered to assess for secondary outcomes, including mortality.

Using propensity score matching, Obaid et al.[86] compared outcomes in patients who received either cryoprecipitate or fibrinogen concentrate as part of their resuscitative strategy. Compared with patients who received cryoprecipitate, those who received fibrinogen concentrate required fewer transfusions and had shorter hospital and intensive care unit lengths of stays. However, mortality was no different.

TABLE 2. Summary of Trials on TXA

Trial	Setting and Study Design	Inclusion Criteria	Cohorts	Findings
Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH 2)[76]	Multicenter, randomized controlled trial across 40 countries	Patients with, or at risk of (as defined by SBP <90 mm Hg or HR >110 beats per minute), significant bleeding	• 1 g of TXA over 10 min followed by an infusion of 1 g over 8 h • Placebo	TXA cohort had lower all-cause mortality and mortality because of hemorrhage
Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS)[79]	Single center, retrospective review; military center in Afghanistan	Patients much have received at least 1 U of PRBCs within 24 h of admission	• 1 g bolus • No TXA	Lower mortality among military personnel who received TXA
Prehospital Tranexamic Acid for Severe Trauma (PATCH)[81]	Multicenter, randomized controlled trial across 15 centers in Australia, New Zealand, and Germany	Patients with a Coagulopathy of Severe Trauma score of 3 or greater	• 1 g of TXA over 10 min followed by an infusion of 1 g over 8 h • Placebo	Prehospital TXA use was not associated with improved functional outcomes 6 mo after injury
Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport (STAAMP) Trial[77]	Multicenter, randomized controlled trial in the United States	Patients who had at least one episode of hypotension (as defined by SBP <110 mm Hg) or HR >110 beats per minute	• 1 g bolus of TXA over 10 min + no additional infusion • 1 g of TXA over 10 min + an infusion of 1 g over 8 h • 2 g of TXA over 10 min + an infusion of 1 g over 8 h • Placebo	Patients who received 2 g of TXA over 10 min followed by an infusion had a lower mortality rate; no differences were noted among patients who received other doses of TXA

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The CRYOSTAT-2 trial addressed the role of early empiric fibrinogen supplementation.[87] This multicenter, phase 3, randomized control trial involved 26 trauma centers in the United States and United Kingdom and enrolled patients who underwent massive transfusion activation or received at least 1 U of any blood component. Patients randomized to the intervention arm received three pools of cryoprecipitate within 90 minutes of hospital admission and within 3 hours from injury in addition to standard care or standard care alone. Those randomized to the standard care arm may have received pools of cryoprecipitate with each cooler delivered. The all-cause mortality rate at 28 days was similar (cryoprecipitate group, 25.3% vs. standard care group, 26.1). In addition, mortality rates at 6 hours and 24 hours were no different, along with the cause of death, with 3.0% of the patients in the intervention arm and 2.5% in the standard care arm dying of uncontrolled bleeding. Deaths due to hemorrhage did occur later in patients who received early cryoprecipitate supplementation (cryoprecipitate group, 191 minutes vs. standard care group, 86 minutes). This study could not demonstrate that early empiric use of cryoprecipitate was associated with improved clinical outcomes. One of the concerns surrounding this study was that patients may not have received cryoprecipitate supplementation in a timely fashion since the median time to first cryoprecipitate transfusion was over an hour from arrival or that sufficient amounts were not given to replete fibrinogen levels. Also, nearly 900 patients were excluded because of the unavailability of a research team, resulting in a convenience sample and potential selection bias.[87]

Although the implications of fibrinogen depletion have been well characterized, the optimal method and dosing of fibrinogen supplementation have yet to be defined.

PROTHROMBIN COMPLEX CONCENTRATE

Repletion of clotting factors is crucial in correcting coagulopathy and achieving hemostasis. Fresh frozen plasma is commonly used to achieve this goal. However, prothrombin complex concentrate (PCC) has been proposed as an alternative solution. Prothrombin complex concentrate provides a concentrated formulation of clotting factors, typically factors II, VII, IX, and X, and was first approved by the Food and Drug Administration in 2013 to manage warfarin-induced coagulopathy.[88]

Using a swine model of hemorrhagic shock in which either a femur or splenic injury was created, Dickneite et al.[89] used either fresh frozen plasma or PCC during the resuscitation phase. The prothrombin time after resuscitation was substantially lower in animals that received PCC. In addition, the time to hemostasis and total volume of blood loss were significantly lower in the PCC cohort.

A single-center retrospective study of all coagulopathic trauma patients, defined by an INR of at least 1.5 on admission, compared FFP with FFP plus PCC.[90] After matching 189 patients who received FFP alone to 63 patients who received FFP plus PCC, the authors noted that INR correction occurred faster in patients receiving PCC (394 vs. 1050 minutes). Those who received PCC required less packed blood cells (6.6 vs. 10 U) and fresh frozen plasma (2.8 vs. 3.9 U) during resuscitation.

A TQIP study from 2011 to 2012 similarly noted that patients who received PCC had a faster INR correction, required fewer units of PRBCs and FFP, and had a lower mortality rate (23.8% vs. 28.0%).[91] The authors also analyzed cost. While PCC was more expensive, the costs associated with transfusions were substantially lower ($7,110 vs. $9,571). The overall hospital cost and charges were unchanged. These studies highlighted the promise of PCC as an adjunct to trauma resuscitation strategies.

A multicenter randomized controlled trial in France involving 12 level I academic trauma centers aimed to characterize the role of PCC in hemorrhagic shock.[92] Any patient deemed at risk for hemorrhage, defined as having received at least 1 U of PRBCs in either the prehospital setting or within the first hour of hospital arrival, an ABC score of at least 2, or if massive transfusion was initiated at the discretion of the managing attending, was eligible for the study. Patients received a single dose of four-factor PCC (4F-PCC) or placebo, in addition to massive

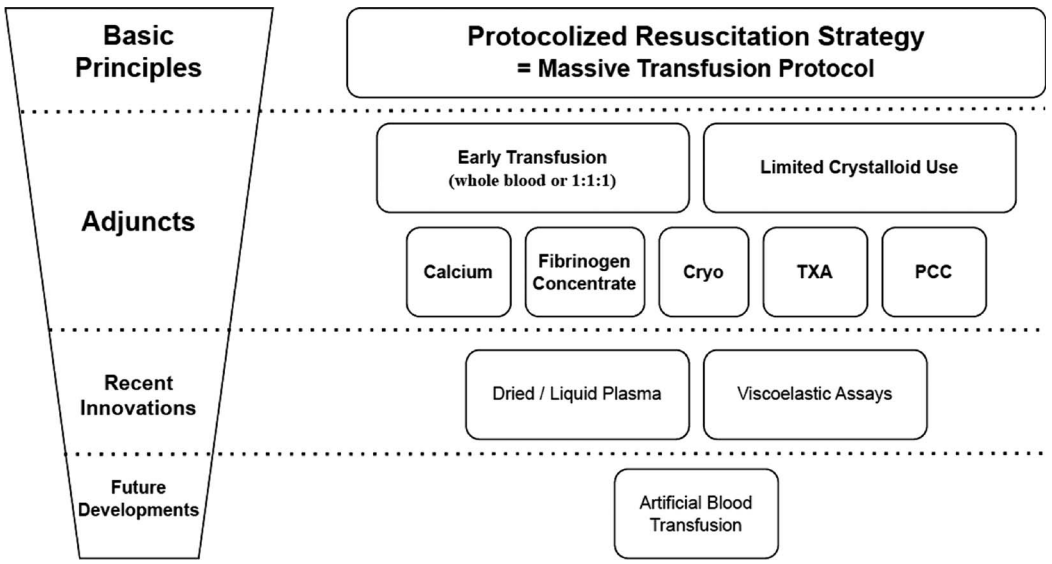

Figure 1. Current and future strategies in fluid resuscitation.

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TABLE 3. Future Investigations and Areas of Research

Knowledge Gaps
1. Is deresuscitation associated with improved outcomes after trauma?
2. Can artificial intelligence better identify patients who need massive transfusion?
3. When is high-volume blood resuscitation futile?
4. Given the limited availability of whole blood, which patients would benefit the most?
5. Which patients benefit from prehospital plasma administration?
6. Can dried plasma or liquid plasma improve outcomes?
7. In which patients is TXA consistently beneficial?
8. What is the optimal method and dosing of fibrinogen supplementation?
9. What is the role of empiric PCC in hemorrhagic shock?
10. Can artificial blood be used in trauma patients?

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transfusion and possibly TXA. The primary outcome of the study was blood product consumption within the first 24-hour period. With more than 300 patients enrolled, the investigators failed to observe a reduction in overall blood product consumption with 4F-PCC usage within the first 24-hour period (4F-PCC, 12 U vs. placebo, 11 U) and no difference in the time it took to correct the INR. Both 24-hour and 28-day mortality were similar. Patients who received 4F-PCC were more likely to experience a thromboembolic event (34.8% vs. 23.1%). The findings of the trial questioned the role of routine use of PCC. However, the study was not designed to look at outcomes with clinical implications such as mortality.

A current double-blinded, phase 3, randomized controlled trial is underway to assess the role of 4F-PCC after traumatic injury, with the primary outcome being mortality.[93] The trial aims to enroll more than 8,000 patients and is expected to conclude in September 2026.

ARTIFICIAL BLOOD

This review article has discussed several blood products; however, all are limited resources, and supply can quickly deplete during a crisis.[94–96] A potential solution is the use of artificial blood. The concept is not new, and interest has existed for decades because of transfusions being associated with transmissible diseases, such as hepatitis C, human immunodeficiency virus, and transfusion reactions. Not requiring blood type compatibility testing and longer shelf lives make artificial blood particularly appealing. There are two formulations of artificial blood: hemoglobin-based oxygen carriers and perfluorocarbon-based products.[97] Hemoglobin-based oxygen carriers require hemoglobin, which allows for oxygen transportation and delivery. The hemoglobin is either isolated from human or bovine blood or synthesized. Hemoglobin-based oxygen carriers, however, do not exert osmotic pressure, which can alter intravascular volume, have short half-lives compared with PRBCs, and release free radicals.[98] Perfluorocarbon-based products are inert molecules that can transport oxygen and carbon dioxide but are associated with complement activation and oxygen toxicity. While the need for artificial blood is apparent, several challenges need to be addressed before it can be used clinically.

CONCLUSION

Aggressive crystalloid resuscitation has been largely abandoned. Emphasis is now given to trauma-induced coagulopathy and restoring a normal coagulation profile. The key principles of contemporary resuscitation are captured in Figure 1. These principles depict the intricacies of maintaining normal coagulation and the multifaceted approach required to achieve this.

Research over the last few decades has been instrumental in identifying factors that contribute to coagulopathy and how to best mitigate them. The trauma community is beginning to unearth how to achieve hemostasis; however, many questions remain. Table 3 lists select questions and areas of future investigation that will help address these knowledge gaps. Many of these questions reflect the optimal use of limited resources and the identification of subpopulations of trauma patients who would benefit from specific interventions.

AUTHORSHIP

R.C. contributed in the conception and study design. N.K.D. and J.K. contributed in the literature review. N.K.D. contributed in the drafting of the manuscript. J.K. and R.C. contributed in the critical revision.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E7).

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